AWARD NUMBER: **W81XWH-14-2-0190**

TITLE: **Testosterone Combined with Electrical Stimulation and Standing: Effect on Muscle and Bone**

PRINCIPAL INVESTIGATOR(S): **GAIL F. FORREST, Ph. D.**

CONTRACTING ORGANIZATION: **Kessler Foundation Inc.**
West Orange, NJ 07052

REPORT DATE: **October 2016**

TYPE OF REPORT: **ANNUAL**

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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5b. GRANT NUMBER
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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Gail F Forrest PhD;

E-Mail: gforrest@kesslerfoundation.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Kessler Foundation

300 Executive Drive, Suite 70
West Orange, NJ 07052-3390

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The study is a prospective, randomized, double blinded, controlled, multi-site clinical trial to determine the efficacy of a tri-combination intervention to improve musculoskeletal gains in men with subacute to chronic SCI with low circulating testosterone levels. Participants will be enrolled at Kessler Foundation (KF), the University of Louisville-Frazier Rehab (UoL), the James J. Peters VA Medical Center (JJPVAMC). During year 2 of the study, the Study Team (Drs. Forrest, Bauman, and Harkema) established a new partnership with a pharmaceutical company (AbbVie) to supply Drug and Placebo for all potential study participants. Each of the study sites submitted to the pharmaceutical company all requested regulatory documentation for supply of drug to all sites. During Year 2, all FDA requirements were satisfied for the acquistion of the IND number for all sites. In addition, the drug/placebo has been manufactured and shipped to the Kessler site (10/23/16). Kessler and JPVAMC received HRPO approval 8/18/16 and 9/1/16respectively. HRPO approval for UoL is pending. Kessler has prescreened 17 participants and currently are screening 10 participants for potential recruitment. Early Year 3 (11/21/16), JJPVAMC will be trained at Kessler on all protocol. JJPVAMC will then start screening, and recruitment of participants.

15. SUBJECT TERMS
Muscle atrophy and osteoporosis after SCI. Testosterone, placebo, multi muscle electrical stimulation, dynamic standing protocol, tri-combination intense therapeutic training.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	22	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION

This study is a prospective, randomized, double blinded, controlled, multi-site clinical trial to determine the effectiveness of a tri-combination Activity-Dependent Rehabilitation Model on improving musculoskeletal gains in men with subacute to chronic SCI who have low serum testosterone levels. A total of 56 research participants will be enrolled across 3 clinical sites: Kessler Foundation Research Center, the University of Louisville-Frazier Rehab and the James J. Peters VA Medical Center (Bronx, NY). Each site will recruit 19 participants over 3 years or 6-7 subjects per year. Eligibility will be determined by the site physician and site PI. Research participants will be randomized into one of four groups: 1) Stand Training only; 2) Stand+Electrical Stimulation; 3) Stand Training+Testosterone; 4) Stand Training+Testosterone+Electrical stimulation. Each research participant will complete 60 sessions of training.

The model involves intense training with testsoterone replacement therapy and electrical stimulation on multiple muscles. Our primary focus is to examine the change in muscle, but we will also look at the change in bone. This tri-combination Activity-Dependent Rehabilitation Model can easily be adapted to a clinic based model.

2. KEYWORDS

Testosterone, multi-muscle electrical stimulation, dynamic standing protocol, muscle volume, MRI, bone mineral density, DXA, QCT scans, metabolic bone markers, subacute SCI, chronic SCI.

3. ACCOMPLISHMENTS

- **What were the major goals of the project?**

Aims of Proposal

The overall aim of this proposal is to determine the interaction of testosterone, ES of multiple leg muscles and stand training or loading (bearing of the body weight) in individuals with subacute to early chronic SCI who are wheelchair reliant at least 75% of the time in a phase I/II multi-site randomized clinical trial (n=56, recruited at 3 training sites) on bone and muscle.

Our primary aim is to assess the effects of our novel tri-combination Activity-Dependent Rehabilitation model approach on muscle volume of the lower limbs.

Our secondary aims are:

i) To better define the mechanisms that contribute to changes in muscle.

Secondary outcome measures associated with this aim will further assess whether the tri-combination of stand training with TRT and ES will lead to increased muscle strength and contractile elements of muscle as shown by an increase in muscle torque, an increased expression of PGC-1α and its downstream targets in the lower limb and an alteration in myostatin signaling. Preliminary data from animal studies have shown increased expression of Activin receptor IIB and increased nuclear localization of Smad2 and Smad3 after SCI and that these adverse changes are reversed by androgens. Additional studies will examine mRNA levels for myostatin, its receptor and its inhibitors (e.g., follistatins) and determine nuclear levels of Smad2 and Smad3. We will also measure resting energy expenditure to confirm that changes in muscles mass correspond to anticipated metabolic effects.

ii) To evaluate the changes in bone and bone structure with Stand Training with TRT and ES.

Secondary outcome measures of this aim will include BMD of the proximal tibia and distal femur; these are the most common sites for fracture and may also respond faster to intervention. Other secondary outcome measures will be BMD at the hip, cortical and trabecular bone with 3-D volumetric measurements, and bone markers for formation and resorption.

- **What was accomplished under these goals?**

In Year 1, a significant obstacle was encountered where we were informed that Watson Laboratories had been acquired by a company that would not be able to supply drug and placebo (the fill details are described on Pages 8-9; in addition, the sequential timeline to a positive solution for acquisition of drug/placebo is also provided on Pages 8-10). Therefore the major accomplishment in Year 1 was on November 10th, 2015 we received notification from Abbvie that they will provide the drug and placebo at no cost to the study. Drs. Forrest and Bauman contacted Dr. Henry on November 11, 2015 to notify her of our final solution. All of these details are described on Page 8-10. In year 1, local IRB at Kessler for original protocol was accomplished, but we placed all IRB submissions and resubmissions on hold until we organized a suitable solution for drug acquisition.

In Year 2, the major accomplishments were: i) the establishment of the contractual agreement between Kessler and Abbvie Inc for drug acquisition according to study protocol and at no cost to the study; ii) The manufacturing of drug and placebo; iii) the shipping of drug to Kessler Pharmacy (arrived 10/17/16); iv) Local IRBs were approved with all changes to satisfy Abbvie and FDA requests for Kessler, JJPVAMC, and UoL; v) HRPO IRB approval at Kessler (8/18/16), JJPVAMC (9/1/16), UoL (pending); vi) Kessler has established a pre screen list and a screen consenting list for potential subjects to be recruited; vii) JJPVAMC will have their training meeting to start grant "11/21/16".

Specific Aims: (1) To examine the effectiveness of stand training with testosterone and electrical stimulation to induce positive changes in muscle volume. **Our secondary aims are:** i) To better define the mechanisms that contribute to changes in muscle. ii) To evaluate the changes in bone and bone structure with Stand Training with TRT and ES.
Note: IRB submissions were modified to show new protocol changes.- see below.

As per SOW	**Timeline**
Major Task 1: Adapt TRT to ES protocol: Complete IRB	
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study 1	
Sites for IRB completions submitted ***Milestone Achieved:*** *i) Initial Local IRB approval for* Kessler, JJPVAMC, UoL	Kessler-12/4/15 JJPMC-1/20/16 UoL`10/27/16
Amendments: ***FDA IND number completed (4/29/15).*** ***Amended and resubmitted to reflect drug/changes.*** ***Final FDA IND number approved 3/3/16.*** ***Amendment to local site IRBs*** Note: In accordance with FDA Request. Each site was required to include a study physician as a co PI. The change is made to each site's IRB. • Review eligibility criteria, exclusion criteria, screening protocol • Finalize amendments to consent form & human subjects protocol • Coordinate with Sites for IRB protocol resubmission • Coordinate with Sites for IRB completions of all amendments. Kessler approval 4/11/16; JJPVAMC approval 1/20/16; UoL 10/27/16	3/3/16 Kessler-4/11/16; JJPMC-1/20/16 UoL-10/27/16
Sites for IRB completions submitted to HRPO ***Milestone Achieved:*** *i) HRPO approval for Kessler,* JJPVAMC (Kessler submitted IRB to HRPO - 5/18/16) ii) ***UoL HRPO IRB submitted 10/31/16***	Kessler- 8/18/16 JJPVAMC- 9/1/16

Major Task 2: Training of protocol at Kessler	3-6
Manual of Operations (MOP) and Standard Operating Procedures for TRT and Case Report Forms completed	6/28/14
Forrest and Harkema trained site PTs on Combination ST+ES. Additional set up of training software and hardware at Kessler for PTs Completed repeatability testing on ES ramping, training procedures to be applied at all sites **JJPVAMC Training meeting for ST+ES training procedures at Kessler**	4/28/15 6/15/16-6/30/16 11/21/16
Dr William Bauman (WB) will train sites to administer testosterone gel based on Standard Operating Procedures.	11/21/16/ Ongoing
Regular biweekly Conference calls (Kessler, UoL, JJPVAMC) established to discuss study protocol, training and testing.	Ongoing
Milestone Achieved: *i)* Kessler and UoL Research staff already trained in standing and ES protocol. ES program automated. *ii)* JJPVAMC schedule to be trained on ES	 JJPVAMC 11/21/16

Major Task 3: Participant Recruitment, Therapy, Participant Evaluation	3-6 after IRB approval
Subtask 1: Data set up with initial subject at each site.	6/28/14
Coordinate with sites for all study steps, data collection and database requirements' - will occur at Training Session at Kessler for JJPVAMC	11/21/16
Set up assessment measurements (already established at 2 sites – Kessler, UoL). JJPVAMC will have kick off meeting 11/21/16	11/21/16/ Ongoing
Begin and continue subject recruitment (Kessler - prescreened 17 subject , currently screening 10 subjects) for recruitment and randomization	9/15/16 Ongoing
Milestone : Evaluate and assign participants to one of the four randomized groups at Kessler	Ongoing
Milestone Achieved: Kessler and JJPVAMC sites: **Study begins**	Kessler 9/15/16; JJPMC11/21/16
Milestone Achieved: 1st participant screen consented ay Kessler	

- **What opportunities for training and professional development has the project provided?**

Training in **Year 1** involved the Kessler PTs working on the Project for preliminary training on using the multi muscle stimulators.

Training in **Year 2** involved Kessler PTs continued work on the Project Training for the multi muscle stimulators to set up all ES training programs and procedures as automated software for all sites.

- **How were the results disseminated to communities of interest?**

Nothing to report

- **What do you plan to do during the next reporting period to accomplish the goals?**

The tasks that we intend to complete in the next year as per the original SOW submitted are given below.

Note: *<u>The time line in the SOW (4.25.16) below will be revised in year 3</u>.**

Major Task 1: Adapt TRT to ES protocol: Complete IRB	Time line (months)
Submit amendments, adverse events and protocol deviations as needed	As needed
Coordinate with Sites for annual IRB report for continuing review	Annually
Milestone Achieved: Local IRB approval at Kessler, UoL , JJPVAMC)	3
Major Task 2: Training of protocol at Kessler	3-6 after IRB approval
Training for ES and drug at Kessler site for JJPVAMC	11/21/16
Dr William Bauman (WB) will train all sites on testosterone gel	11/21/16
Forrest, Harkema and Bauman will continually instruct all sites on protocol description per MOP	11/21/16 and ongoing
Milestone Achieved: Research staff trained	11/21/16 and ongoing
Subtask 2: Site Visit to review training	4 -5
Drs. Forrest will visit the Bronx VAMC study site to provide review and potential additional instruction of the procedures for Stand Training with ES (December 2016, January , 2017 and as required). This will be followed by ongoing conference calls.	4 -5
Milestone Achieved: Maintained protocol training and follow up at all sites.	4 -5
Major Task 3: Participant Recruitment, Therapy, Participant Evaluation	25-30
Subtask 1: Continue Data set up with subjects at each site	Timeline after IRB approval
Continue to Coordinate with sites for all study steps, web data collection and database requirements : Continue with assessment measurements at all sites	4-6
Milestone Achieved: 1st participant consented, screened and enrolled at ***<u>all sites</u>*** *Kessler site completed first screen in 2016; JJPVAMC will complete after 11/21/16 meeting;*	4-6
Milestone Achieved: All sites Study begins	4-6
Continue subject recruitment	4-30
Continue Screen potential participants	4-30
Evaluate and assign participants to one of the four randomized groups	4-30
Outcome measures assessment at each time point continues	4- 30
At all sites: Research participant complete 60 sessions of training frequency of 4 times per week (1.5-hour) followed by post testing and follow up (MRI, DXA)	4- 33
Milestone Achieved: Record data for year 1, 2, 3, into ITW database; Report initial findings	4-33
Milestone Achieved: Report findings from Clinical Trail	33-36
Major Task 6: Data Analysis	
Subtask 1: Coordinate with Sites & Data Core entry for monitoring data collection rates and data quality	4-33

Data analyses ongoing for outcome measures (Muscle volume, muscle torque, gene expression, myostatin signaling, BMD, bone and blood markers, volumetric measures of bone resting energy expenditure)	6-33
Milestone Achieved: Report results from data analyses	35-36

4. IMPACT

Nothing to report

5. CHANGES/PROBLEMS

- **Changes in approach**

No change in protocol in Year 1 or in Year 2

- **Actual or anticipated problems or delays and actions or plans to resolve them**

During the reporting period in Year 1 there were significant delays associated with acquisition and delivery of drug/placebo. These delays were reported in the quarterly reports. The delays are outlined in detail below:

As reported in Quarter 1, year 1 report the main problem to address for Quarter 1 in year 1 was that we were informed that* Watson Laboratories *had been acquired by a company that would not be able to supply drug and placebo for our proposed placebo-controlled RCT.
For the Year 2, Quarter 1 report we proposed our final solution to the TRT/Placebo issue.

- At the time of submission of our grant, Watson Laboratories had provided a letter of support which stated that this company would provide TRT patch and matching placebo for our study. The support being offered by Watson Laboratories was a continuation of previous collaboration with the company for similar work that was completed by Dr. William A. Bauman, co-principal investigator on the current grant, which addressed the safety and efficacy of TRT patch in a population of persons with chronic spinal cord injury at the James J. Peters VA Medical Center and The Kessler Institute for Rehabilitation, work which was published in *Hormones and Metabolic Research* in 2011. In our Quarter 1, Year 1 report we reported that Watson Laboratories was obtained by Actavis Pharmaceuticals, and management at the new company had informed us that they had decided not to provide study drug for our RCT, nor for any other RCTs at this time. It was inferred that their policy decision was based on a change in philosophy toward research initiatives which took into account the total cost of supplying matching placebo and the assumption of risk for any new study.

- After careful consideration and in discussion with Patricia Henry, PhD, Science Officer (discussions: 2/17/2015 and 4/1/2015) Drs. Forrest, Bauman, and Harkema addressed the problem in a satisfactory manner to maintain the study as designed and to make no changes to the SOW.

- In Quarter 1, we reported that the FDA approved New York based compound pharmacy "Metro Drugs" would be supplying the drug (Gel) and placebo to the sites, and we provided a letter from the company confirming this agreement. Shortly after we submitted the Quarter 1 report, we were informed by the New York State (NYS) DEA that the only suitable and legal option to supplying drug and placebo to our 3 study sites was FDA approved pharmacy that was located outside NYS because of stringent laws that prohibited the dispensing of any controlled substances by an appropriately licensed NYS pharmacy outside of the state. In actual practice, the testosterone/placebo preparation would be sent by the FDA pharmacy directly to the subjects.

- As you may appreciate, identifying a FDA compound pharmacy that has the experience and resources to supply both study drug and placebo, with an appropriate dispensing system in place, was an onerous task, and this was, at the time, our main difficulty with being able to initiate the study. A pharmacy was located and agreed to provide the investigators with drug and placebo. To do so required the investigators to pay for the cost of topical generic testosterone preparation (at approximately 25% the cost of Androderm) and for a placebo gel. The cost of these preparations had been provided in a previous email, as well as the other associated costs, including those of the cost of dispensing ($10,920), repacking ($6006), and shipping ($24,570), with a total final cost of the pharmacy to provide us with drug/placebo of over $100,000, an expense that were not budgeted prior to Watson Laboratories withdrawing their support for our proposal. Of note, the investigators decided that intramuscular preparations of testosterone were not physiologic (peaks and valleys in pharmacokinetics) and in the SCI population would be associated with a heightened risk of autonomic dysreflexia, potentially a life-threatening complication, if the injection is delivered below the level of lesion; administration of the intramuscular injection above the level of lesion may be associated with pain and discomfort upon transfers, which may limit mobility, reduce drug/placebo compliance, and increase drop-out rates. A total of 56 research participants is proposed to be studied in our proposal.

- The source of the drug was Belmar Pharmacies, a licensed non-resident pharmacy (license #30,649) and that is licensed with the DEA. **The letter was provided in the Quarterly report dated 7/14/15.** The pharmacy would have supplied the patient-specific compounded testosterone or placebo, directly to patients based upon a valid prescription. To date, this company had been the only viable option after an exhaustive search of both Clinical Trials.gov and reaching out to other pharmacies. Drs. Forrest and Bauman worked with the company to set up the standard of operation procedures for dispensing the drug/placebo to study participants.

- Drs. Forrest and Bauman had been in discussions via several email correspondences and conference calls (6/9/15; 6/15/15; 6/16/15) with Patricia Henry, Ph.D., Science Officer, regarding the potential of additional funds to cover the additional cost of the drug. Based on our discussions, Dr. Henry instructed us to submit a formal request for additional funding (6/18/15).

- Drs. Forrest and Bauman submitted a formal request to the DOD for additional funding on 6/23/15. **Please see letter in report dated 7/14/15.**

- Of note, in January 2015, the investigators submitted a request to Abbvie to provide testosterone gel and matching placebo for the study. We considered this "option" to be a real possibility, albeit somewhat unlikely if one considers the length of time that our request had languished without resolution. However, our proposal continued to be actively considered. We suggested in our previous quarterly report (7/14/2015) that if this company approved our request, then the investigators would proceed with the clinical trial without the need for additional financial support from the DoD.

- Fortunately, on November 10th, 2015 notification was received from Abbvie that the company had agreed, in principle, to provide the drug and placebo at no cost to the study. Drs. Forrest and Bauman contacted Dr. Henry on November 11, 2015 to notify her of our final solution. Dr. Henry had requested that Dr. Forrest submit a revised SOW to Dr Henry on 11/23/15. Based on the revised SOW (4/25/16. Year 1 Final report) – we have amended the protocols at all institutions to comply with our proposed changes in drug formulation (e.g., patch to gel application), dosage, and origin of agent/placebo.

- ***During the reporting period in Year 2:***

  - Abbvie Inc. have manufactured drug/placebo at no cost to the grant. Final contractual agreement between Kessler Foundation and Abbvie was signed 6/26/16 (details Q3, Year 2) .

  - All details associated with shipping of drug to each site, storage of drug, administration have been addressed in Q2, Year 2.

  - Final delivery to drug to Kessler has occurred on 10/23/16.

- An additional delay to final IRB approval in Year 2 was the acquisition of the IND number from the FDA and the modification of protocol, as requested by the FDA. This was accomplished by 3/3/16 at Kessler.

- **Changes that had a significant impact on expenditures**

Because of the unanticipated delay in our obtaining of drug/placebo, the projected funds for Year 1 and Year 2 have not been expended. These details were outlined both in our financial and quarterly reports.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

No significant change to human subjects

6. PRODUCTS

None to report

- **Publications, conference papers, and presentations**

None to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report

- **What individuals have worked on the project?**

In Year 2 period individuals' have worked primarily on setting up the protocol, IRB submissions, Manual of Operation Procedure (MOP) and Case Report Forms (CRF) and recently pre screening and screen consenting of subjects. In addition Physical Therapists and engineers have worked on the establishment of the SAGE automated ES program for the standing +ES protocol

Overall Submitting PI: Gail F Forrest Ph.D.
Co- PI: William A. Bauman, M.D.

Individuals that have worked for at least 1 month (~160 hrs) in year 1.

Name: Milda Woods
Project Role: Study Coordinator, consultant
Nearest person month worked: 3.6months
Contribution to Project: Ms. Woods has worked continually with Dr Forrest in year 2:

i) On the setting up of the re application to the FDA for all documentation required to gain the IND number. The active IND number was required by all local IRBs and before submissions to the HRPO for approval.
ii) On all documentation for Abbvie Inc submission approval process. There were several iterations of submitted paper work to the drug company.

iii) On all of the submissions to the HRPO for all IRB approvals.
iv) On all case report forms for subject binders for all sites and Manual of Operations to be used at all sites.

Name: Erica Garbarini
Project Role: Physical Therapist
Nearest person month worked: 1 month.
Contribution to Project: Ms Garbarini has worked continually with Dr Forrest in year 2

i) On setting up the stimulation protocol using the Sage Stimulator device (as described in original protocol). The system will allow for standardization of multi muscle electrical stimulation training during stand training at all sites.
ii) Modification of Case report forms and daily training sheets for subject folders and Manual of Operating Procedures.

Other Support: New Jersey on Spinal Cord Injury Research, Rehabilitation Engineering Research Centers (RERC) National Institute on Disability, Independent Living and Rehabilitation Research

- **What other organizations have been involved as partners?**

Site 2: University of Louisville (UoL)
Frazier Rehab Institute
220 Abraham Flexner Way, Suite 1506
Louisville, KY 40202
Site PI: Susan Harkema Ph.D.
Site 3: James J. Peters VA Medical Center (JJPVA)
130 West Kingsbridge Road
Bronx, NY 10468
Site PI: Ann Spungen. EdD. William Bauman.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Provided below:

Gail Forrest Ph.D
90RE5021 (Foulds, PI) 9/30/15 – 9/29/21 .60 CM (5%)
NIDILRR. RERC $159,331 (Annual Directs)
Subrecipient Agreement $995,821 (Total Award)
From New Jersey Institute of Technology
Forrest (Site Project PI)
Site Project: Exoskeleton and spinal cord stimulation for SCI

Forrest: SC140099 (**Forrest Co-I**; Bloom, PI,) 9/30/15 – 9/29/19 .60 CM (5%)
USAMRAA/CDMRP/DoD $52,669 (Annual Directs)
Subrecipient Agreement from Feinstein Institute $236,693 (Total Award)
Biomarkers of Spontaneous Recovery from Traumatic Spinal Cord Injury

1R21NS095052 (**Forrest Co-I**, Jiang, PI) 4/1/16 – 3/31/18 .60 CM (5%)
NIH $137,468 (Annual Directs)
Longitudinal Assessment of Spinal Cord Structural Plasticity using DTI in SCI Patients

William Bauman MD

VA RR&D #B9212-C Bauman (PI) 07/16-06/21
National Center Grant $2,250,000
Center of Excellence for the Medical Consequences of Spinal Cord Injury
Role: Director/Principal Investigator

Role: PI Federal #2003 Bauman (Co-Chairman) 10/15-9/20
VA Cooperative Study $23,000,000
Title: Exoskeleton Assisted-Walking (EAW) in Veterans with SCI: Impact on Quality of Life
Role: Co-Chairman

Ann Spungen PhD
Role: PI Federal #2003 Bauman (Co-Chairman) 10/15-9/20
VA Cooperative Study $23,000,000
Title: Exoskeleton Assisted-Walking (EAW) in Veterans with SCI: Impact on Quality of Life
Role: Co-Chairman

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS submitted in appendices

9. APPENDICES

PIs Bio has been included.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Gail F Forrest

eRA COMMONS USER NAME (credential, e.g., agency login): gfforrest

POSITION TITLE: Associate Director, Human Performance and Engineering(HPE).

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bachelor of Applied Science RMIT, Melb., Australia	B. App. Sc	12/1979	Mathematics/Computing
Temple University, Philadelphia	Ph.D.	1/2001	Biomechanics
Post Doctoral Fellow, Kessler Foundation		1/2001-12/2002	Biomechanics

1 B. Positions and Honors

Prior to 1989	Mathematics and Computer Science Senior Level Teacher, Australia.
1989-1992	Corporate Consultant to Four Season Hotels (Daikyo Corporation), Australia and Japan.
1991-1992	Victoria University, Melbourne, Australia, Grad Dip. Biomechanics
1995-1997	Teaching Assistant - Human Anatomyand Biomechanics, Temple University.
1997-1998	Biomechanics Lecturer and Coordinator, Temple University.
1998-1999	Teaching Assistant – Physiology, Biomechanics, and Anatomy, Temple University
1999-2000	Research Assistant – "Dynamic Control of Head Stability in Older Adults" Grant (NIA # RO3), Physical Therapy Dept, Temple University.
2000-2002	Post Doctoral Fellow, Kessler Medical Rehabilitation Research and Education Corporation,West Orange, NJ.
2003-2007	Research Scientist II , Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ.
2007- 2012	Interim Director, HPMAL , Kessler Foundation Research Center , West Orange, NJ.
2007- Date	Kessler site Director of the NeuroRecovery Network.
2012- 2014	Assistant. Director Human Performance Laboratory, Kessler Foundation.
2014- Current	Associate Director Human Performance and Engineering, Kessler Foundation.

University Appointments

5/2000-9/2000	Adjunct Professor Biomechanics, Physiology, – Temple University, University of Pennsivalia
1/2001-6/2005	Instructor, University of Medicine and Dentistry of New Jersey / New Jersey Medical School
7/5/05-present	Assistant Professor University of Medicine and Dentistry of New Jersey/New Jersey Medical Sc.
2011-Date	Affiliated Faculty Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ
2012- Date	Member of the Graduate Faculty in Biomedical Science, University of Medicine and Dentistry of New Jersey, Newark, NJ.
2013 –Date	Associate Professor Rutgers New Jersey Medical School, Rutgers, the State University of New Jersey

Other Professional Experience

1999 - 2000	Research Assistant Dynamic Control of Head Stability, Agency NIH/NIA (RO3); (Ronita Cromwell, Ph.D., Principal Investigator)
2001 - present	Institutional Review Board Member Kessler Foundation
2004 - present	Reviewer for Journal of Neuroengineering and Rehabilitation
2005 - present	Reviewer of Journal of Rehabilitation Research and Development

2005 - present	Reviewer of Journal of Spinal Cord Medicine
2005 - present	Compliance Committee member (subcommittee of IRB)
2005 - present	Committee member for ACRM International task force
2005 - present	Reviewer, RESNA
2009 -present	Reviewer NIH (2014/10 ZRG1 BBBP-Y (05), Motor Function, Speech and Rehabilitation (MFSR) Study Section).
2011-present	Craig H Neilson Foundation
2013-present	Reviewer for Gait and Posture.

2 c. Contribution to Science

1. My dissertation concentrated on understanding the dynamics of walking for older and younger adults using kinematics and muscle activation and intersegmental dynamics of the lower limbs;
    - **i.** Cromwell R.L., Newton, R. A., **Forrest, G.F.** Influence of vision on head stabilization strategies on older adults during walking. Journal of Gerontology: Medical Sciences, , 57(7),: M442-8, 2002.
    - **ii.** Cromwell, R.L., Newton, R.A., **Forrest, G**. Head stability in older adults during walking with and without visual input. Journal of Vestibular Research, 11(2): 105-14, 2001.
    - **iii.** Cromwell, RL, Newton, RA, **Forrest, G.** Age related changes in head stabilization during walking under altered visual conditions. In Duysens, J, Smits-Engelsman, BCM, Kingma, H, (eds) Control of Posture and Gait. Symposium of the International Society for Postural &Gait Research, Maastricht, The Netherlands, 86-90, 2001.
    - **iv.** Straub, S.J., Tierney, R.T., Hamstra, K., **Forrest, G. F.,** Swanik, C.B. (2001). Accuracy and Reliability of the Peak Motus Motion Analysis System; Journal of Athletic Training 36, 2.
2. My postdoctoral fellowship work contributed to the scientific understanding of neural plasticity in the lower limbs after intense locomotor step training intervention using a treadmill with body weight support for both motor complete and incomplete SCI. For all of this dissertation work we utilized a full body kinematic marker set and lower extremity muscle activation to study the effect of the intervention on treadmill gait and as well we studied postural control using kinematics and muscle firing patterns of the lower limb.
    - **i.** **Forrest, GF**, Sisto, SA, Kirshblum, S., Asselin, P, Mores, J, Bond, Q, Lafountain, M, Harkema, S. Locomotor training with incremental changes in velocity: Muscle and metabolic responses, Topics in Spinal Cord 29(4), 464-466, 2008
    - **ii.** **Forrest, GF**, Sisto, SA, Barbeau, H, Kirshblum, S, Wilen, J., Bond, Q., Bentson, S., Asselin, P, , Harkema, S. Neuromotor and Musculoskeletal Responses to Locomotor Training for Individuals with Chronic Motor Complete, ASIA-B Spinal Cord Injury. J Spinal Cord Med 2008; 31(5):509-21.
    - **iii.** Sliwinski, M.M., Sisto, S.A., Batavia, M., Chen, B. and **Forrest, G**. . Dynamic stability during walking following total unilateral hip arthroplasty. Gait & Posture 19(2):141-147. 2007.
3. We evaluated the intense locomotor training intervention in an outpatient clinical program for over 250 patients across seven treatment centers in the USA.
    - **i.** **Forrest GF,** Hutchinson K, Lorenz DJ, Buehner JJ, Vanhiel LR, Sisto SA, Basso DM. Are the 10 Meter and 6 Minute Walk Tests Redundant in Patients with Spinal Cord Injury?. PLoS One. 2014 May 1;9(5)/2014
    - **ii.** **Forrest, GF,** Hudson, L, Basso, M, Behman, A, Harkema, SJ, Correlations among functional outcome measures in patients with incomplete spinal cord injury who are receiving activity-based locomotor gait training rehabilitation. Archives of Physical Medicine and Rehabilitation. 2012 Sep;93(9):1553-64
    - **iii.** Morrison, SA, **Forrest, GF**, VanHiel LR, DeLorenzo,D. NeuroRecovery Network Provides Standardization of Locomotor Training for Persons With Incomplete Spinal Cord Injury. Archives of Physical Medicine and Rehabilitation. 2012 Sep;93(9):1574-7.
    - **iv.** Buehner J, **Forrest GF**, Schmidt, M, Tansey K, Basso M. Relationship between ASIA Exam and Functional Outcomes in the NeuroRecovery Network Locomotor Training Program. Archives of Physical Medicine and Rehabilitation. 2012 Sep; 93(9):1530-40.
4. Our more recent research has been concentrated on multi muscle stimulation combined with dynamic stand training using bodyweight support and we studied the neuroplasticity effect of the intervention on kinematics and muscle activation during stepping on the treadmill and overground gait.
    - **i.** Pilkar RB, A, Yarossi M, **Forrest G** Application of Empirical Mode Decomposition Combined with Notch Filtering for Interpretation of Surface Electromyograms during Functional Electrical Stimulation Transactions on Neural Systems & Rehabilitation Engineering Accepted 2016

ii. Pilkar R, Ramanujam A, Garbarini E, **Forrest GF**, "Validation of Empirical Mode Decomposition Combined with Notch Filtering to Extract Electrical Stimulation Artifact from Surface Electromyograms during Functional Electrical Stimulation", *Proceedings of IEEE Eng Med Bio Soc* 2016.

iii. Canton S, Momeni K, Ramanujam A, Garbarini, A, **Forrest GF**. Neuromotor Response of the Leg Muscles Following a Supine, Stand Retraining With/without Neuromuscular Electrical Stimulation Training Intervention for Individuals with SCI: A Case Series. *Proceedings of IEEE Eng Med Bio Soc* 2016

iv. Momeni K, Canton S, Ramanujam A, Garbarini, A, **Forrest GF**. Effects of Lower Limb Electrical Stimulation on Trunk Stability in Persons with SCI During Walking. *Proceedings of IEEE Eng Med Bio Soc* 2016.

v. Pilkar RB, Yarossi M, **Forrest G**. Empirical mode decomposition as a tool to remove the function electrical stimulation artifact from surface electromyograms: preliminary investigation. IEEE Engineering in Medicine and Biology Conference Proceedings 2012; 1847-50. doi: 10.1109/EMBC.2012.6346311.

5. In addition we have focused on Wearable Robotics research and the effect on gait. We are currently investigating multiple wearable robotic exoskeletons and the training effect on neural and gait recovery both within and outside the exoskeleton as well as investigating the effect on muscle and bone. Our contributions to science encompass the training effect of these devices as a suitable device to be used in the community or as a device that can effectively be used in the clinic or understanding the the health benefits associated with using the powered robots.

i. **Forrest GF**, A, Cirnigliaro C. Muscle Activation and kinematic coordination during Exoskeleton Assisted Walking. Under Review to Frontiers in Neuroscience, 2016.

ii. Ramanujam A, Spungen A, Asselin P,Garbarini E, Augustine J Canton S, Barrance P, Forrest GF. .Training Response to Longitudinal Powered Exoskeleton Training for SCI The International Symposium on Wearable Robotics *18-21 October, 2016. La Granja, Segovia, Spain Published* http://www.springer.com/us/

iii.

3 D. Research Support

Active Research Support

90RE5021-01-00 Rehabilitation Engineering Research Centers (RERC)
Forrest (project PI) 9/30/15 – 9/29/21
National Institute on Disability, Independent Living and Rehabilitation Research
Site Project: Exoskeleton and spinal cord stimulation for SCI:
We propose that the combination of interventions of the exoskeleton assisted walking (EAW) with transcutaneous lumbosacral stimulation (TLS) would increase the excitability of the cord and afferent input when training in the exoskeleton to increase lower extremity muscle firing and to functionally increase walking speed.

W81XWH-14-2-0190 Department of Defense PI Forrest 9/1/14-8/30/18
USAMRAA/CDMRP/DoD
Testosterone combined with Electrical Stimulation and Stand Retraining.
A Phase I/II prospective, randomized, double blind, controlled, multi-site clinical trial where the primary aim is to determine the neurological and neuromuscular interaction of testosterone, neuromuscular stimulation of multiple lower limb muscles and loading in individuals with sub acute to early chronic SCI who are non ambulatory. Ultimately we are interested in recovery of muscle and bone and the effect on functional motor gain for chronic SCI.

B1-2015-PP PI Harkema Forrest (Co-I) 3/4/15 – 3/4/2020
Christopher Dana Reeves Foundation.
BIG Idea Project: Recovery of Autonomic control of cardiovascular and bladder function and the ability to stand and voluntary leg control movements below the level if injury with epidural stimulation
The objective of the project is to test the hypotheses related to neural control of human movement and cardiovascular function after human spinal cord injury while also obtaining knowledge for optimizing spinal cord epidural stimulation (scES) as a therapeutic intervention that can be immediately translated to larger numbers of patients who now have no treatment options for the secondary consequences of spinal cord injury.

SC140099 Department of Defense PI Bloom; Site PI Forrest 9/30/15 – 9/29/19
USAMRAA/CDMRP/Department of Defense
Biomarkers of Spontaneous Recovery from Traumatic Spinal Cord Injury

The objective is to test the hypothesis that levels of some inflammatory biomarkers correlate inversely with functional recovery throughout the first year after spinal cord injury (SCI). The project specific aims are to (1) identify the circulating inflammatory response in patients with SCI, (2) determine the trajectory of spontaneous functional recovery in patients with SCI, and (3) derive a predictive, multiscale model of functional recovery after SCI.

W81XWH-14-2-0170 PI Spungen – Site PI Forrest 9/1/2014-8/30/2017
USAMRAA/CDMRP. Department of Defense
A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function, and Cardiometabolic Profiles in Persons with SCI"
The primary objectives of this research is to document how long it will take to reach functional gains, such as speed and distance after 36 sessions of training with these devices. Preliminary studies support the goals that walking in the exoskeletons will improve bowel function and body composition.

CSCR13IRG013 Forrest (PI) 6/17/2013-6/16/2017
New Jersey Commission on Spinal Cord Research)
Non-ambulatory SCI walk using a Robotic Exoskeleton: Effect on bone and muscle
The overall purpose of this pilot study is to assess if 5 hours per week for 20 weeks of exoskeleton-assisted walking over ground for persons with chronic SCI will positively affect the musculoskeletal system. In addition we will evlaute the human neuromuscluar and mechanic reposne to the robot.

H133N110020 Forrest (Co-PI) 10/01/2011 – 9/31/17
NIDRR Models Systems Primary Research Project
Restoring Lost Functions after Spinal Cord Injury: Combination Therapy with Dalfampridine and Locomotor Training for Persons with Chronic, Motor Incomplete Spinal Cord Injury.
The primary purpose of this National Institute on Disability and Rehabilitation Research funded project is to examine the effect of combination of Dalfampridine and Locomotor Training on walking distance and musculoskeletal system.

1R21NS095052-01A1 Jiang T (PI) Forrest (Co-I) 4/1/16 – 3/31/18
NINDS.
Major goal is to complete Longitudinal Assessment of Spinal Cord Structural Plasticity using DTI in SCI Patients

CSCR15ERG013NJC: Jiang T (PI) Forrest (Co-I) 6/29/2015-6/30/2017
New Jersey Commission on Spinal Cord injury
The major goal is assessing Spinal Cord Structural Changes using Diffusion Tensor Iimaging in Patients with Incomplete Traumatic Spinal Cord Injury

143298 Forrest (Co-PI) /01/7 – 9/31/16
NIDRR
Advanced Rehabilitation Research and Training Center (ARRTC) on Neuromusculoskeletal Rehabilitation Post-Doctoral Training Grant.
The purpose of this NIDRR funded ARRT project is to provide research training and experience at an advanced level to individuals with doctorates or similar advanced degrees who have clinical or other relevant experience.

07-3063-SCR-E-0 Forrest (Co-PI) 01/01/7 – 1/31/17
Center For Disease Control and Christopher Dana Reeves Foundation
NeuroRecovery Network grant.
The major goal of this project is to develop specialized centers that provide standardized activity-based therapy care based on current scientific and clinical evidence for people with SCI and other selected neurological disorders.

CSCR14ERG007 Pilkar (PI) Forrest (Co-I) 10/17/2014-9/16/2017
New Jersey Commission on Spinal Cord Research
Development of Signal Processing Toolbox for Assessing Neuromuscular Response during Electrical Stimulation.
The goal of this study is to develop a robust signal processing algorithm to extract EMG during ES and study the physiological significance of ES on neuromuscular properties of the stimulated muscle. The outcomes of this study will help in understanding the direct effects of ES on muscles by getting access to high quality EMG during ES and help the clinician or researcher to modify and optimize FES training paradigms based on the target muscle response

Completed Research Support

Parker Hannifan **Forrest (Site PI)** **10/17/2014-9/16/2015**
Indego® Exoskeleton; Assessing Mobility for Persons with Spinal Cord Injury (SCI).
***Two separate protocols are under the one title; *PH-INDO1 (FDA) and *PH-IND02 (Exploratory)**
Description of Project:
The purpose of this project is to evaluate if the Indego® robotic device is both safe and effective at allowing persons with SCI who are non-ambulatory or poorly ambulatory to stand up and walk under a variety of conditions; indoor surfaces, outdoor surfaces, elevators, managing doorways, different seat heights and extended distances.

NJCSCR13FEL009 **Forrest (Co-I)** **10/17/2014-9/16/2015**
New Jersey Commission on Spinal Cord Research
Quantitative Measure of Force During Electrical Stimulation: An Exploratory Study
Non-ambulatory SCI walk using a Robotic Exoskeleton: Effect on bone and muscle
The overall purpose of this pilot study is to assess the muscle activation, 3D forces and moments generated at the knee during ES induced contraction during standing for motor complete SCI. **Mentor:** Forrest GF
Mehmed Bugrahan Bayram (PI)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: BAUMAN, William A, MD

eRA COMMONS USER NAME (credential, e.g., agency login): WBAUMAN

POSITION TITLE: Professor of Medicine and Rehabilitation Medicine; Director, Center for the Medical Consequences of SCI, Co-Investigator

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Harvard College, Boston, MA	B.A.	06/1972	English
State University of New York, Downstate College of Medicine, New York, NY	M.D.	06/1976	Medicine

1 B. Positions and Honors

1.1 Positions and Employment

1982 – 1987	Associate Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY
1983 – 1985	Attending Consultant, Department of Medicine, VA Medical Center, Bronx, NY
1985 – 1989	Physician/Research Associate, Solomon A. Berson Research Laboratory, VA Medical Center, Bronx, NY
1987 – 1989	Associate Professor of Medicine and Rehabilitation, Mount Sinai School of Medicine, New York, NY
1989 – 2003	Director, Spinal Cord Damage Research Center, Mount Sinai Medical Center, New York and VA Medical Center, Bronx, NY
1996 – Present	Professor of Medicine, Mount Sinai School of Medicine, New York, NY
1996 – Present	Professor of Rehabilitation Medicine, Mount Sinai School of Medicine, New York, NY
2001 – Present	Director, VA Rehabilitation Research & Development Center of Excellence for the Medical Consequences of Spinal Cord Injury, James J. Peters VA Medical Center, Bronx, NY

1.2 Other Experience and Professional Memberships

1976 – 1977	Medical Internship, New York University Medical Center, New York, NY
1977 – 1979	Medical Residency, Montefiore Hospital & Medical Center, Bronx, NY
1979 – 1980	Endocrine Fellowship, VA Medical Center, Bronx, NY
1980 – 1982	Endocrine Fellowship, Montefiore Medical Center, Bronx, NY
1982 – 1985	NIH SERCA Recipient, Attending, Departments of Medicine and Endocrinology & Clinical Sciences, Montefiore Medical Center, Bronx, NY

1.3 Honors

1972	Honors graduate in English Literature, Harvard University
1982	Recipient of NIH Special Emphasis Research Career Award
1994	Excellence in Medical Research, Medical Service, VA Medical Center, Bronx, NY
2001	William Dock Award for outstanding teaching ability in Internal Medicine/Endocrinology
2002	Excellence Award in Research (American Paraplegia Society)
2005	Paul B. Magnusson Award, VA RR&D Service
2014	Medalist, Samuel J. Heyman Service to America Award, Science & Environment

2 C. Contribution to Science

1. Osteoporosis and fractures present a major problem for persons with SCI. My contributions include defining calcium metabolism and bone disease in persons with SCI. Our publications first suggested a high prevalence of vitamin D deficiency in persons with SCI and proposed an approach for vitamin D replacement therapy. Despite literature that suggested a value to bisphosphonate therapy in those with SCI, possibly because of the work conducted in those with

varying completeness of lesion, our work has demonstrated the limited efficacy of bisphosphonates administration in persons with acute complete motor SCI, necessitating the search for more effective therapeutic approaches. Our work in monozygotic twins, discordant for SCI, has suggested that bone loss continues for decades after initial injury, a new and controversial finding. We have shown that bone mass below the level of lesion is directly associated to body fat, and also directly correlated to the serum estradiol levels. Our group has provided evidence of the cellular, biochemical, and molecular effects of paralysis due to SCI or nerve transaction on bone.

a. Bauman WA, Spungen AM, Schwartz E, Wang J, Pierson RN Jr. (1999) Continuous Loss of Bone in Chronic Immobilization: A Monozygotic Twin Study. *Osteoporos Int*. 10:123-127.
b. Bauman WA, Spungen AM, Wang J, Pierson RN, Schwartz E. (2006). Relationship of Fat Mass and Serum Estradiol with Lower Extremity Bone in Persons with Chronic Spinal Cord Injury. *Amer J Physiol Endocrinol Metab*. 290(6):E1098-103.
c. Bauman WA, Cardozo C. (2014). Osteoporosis in Individuals with Spinal Cord Injury. *JM R*. S1934-1482(14):1358-1366.
d. Bauman WA, Cirnigliaro CM, LaFountaine MF, Kirshblum SC, Spungen AM. (2015). Zoledronic Acid Administration Failed to Prevent Bone Loss at the Knee in Persons with Acute Spinal Cord Injury: An Observational Cohort Study. *J Bone Mineral Metab*. 33(4): 410-421.

2. Although it would appear intuitive that individuals who have adverse body composition and reside at the lowest end of the activity spectrum would have metabolic problems which predispose to cardiovascular disease, prior to our group's entrance to the field, little had been reported in the literature. My contribution has been to be the first investigator to systematically study carbohydrate and lipid metabolism in persons with SCI and suggest that the abnormalities observed would be anticipated to predispose to premature cardiovascular disease. Prior to this work, it was unclear that persons with SCI had disorders of carbohydrate metabolism, which has since been characterized by a high prevalence of carbohydrate intolerance and diabetes mellitus. The finding of low high-density lipoprotein (HDL) cholesterol in those with SCI was observed by our group and subsequently confirmed by others. By nuclear medicine technology and electron beam computerized tomography, publications demonstrated the likelihood of premature atherosclerotic disease in those with SCI. Recently, we have reported on the blunted action of insulin on the sublesional microvascular.
   a. Bauman WA, Spungen AM. *(*1994). Disorders of Carbohydrate and Lipid Metabolism in Veterans with Paraplegia or Quadriplegia: A Model of Premature Aging. *Metabolism*. 43:749-756.
   b. Bauman WA, Adkins RH, Spungen AM, Herbert R, Schechter C, Smith D, Kemp B, Waters RL. (1999). Is Immobilization Associated with an Abnormal Lipoprotein Profile? Observations from a Diverse Cohort. *Spinal Cord*. 37:485-493.
   c. Bauman WA, Adkins RH, Spungen AM, Waters RL. (1999). The Effect of Residual Neurological Deficit on Oral Glucose Tolerance in Persons with Chronic Spinal Cord Injury. *Spinal Cord*. 37:765-771.
   d. La Fountaine M, Rosado Rivera D, Radulovic M, Bauman WA. (2013). The Hemodynamic Actions of Insulin are Blunted in the Sub-lesion Microvasculature of Healthy persons with Spinal Cord Injury. *American Journal of Physical Medicine & Rehabilitation.* 92(2): 127-135.

3. Persons with SCI immediately lose muscle and gain fat after injury. Prior to our work, there had been a paucity of rigorous body composition studies. My contribution to body composition in persons with SCI has been to compare various methodologies to determine body adiposity, develop or apply innovative methodologies, define body composition changes after acute and in chronic injury, and more clearly delineate the relationship of body composition to metabolic derangements. A portion of this work, which was performed in monozygotic twins, one in each pair discordant for SCI, and in cross-sectional studies that have served to define changes in soft tissue mass over decades of life in persons with SCI, has improve our general knowledge in this area of study. The loss of muscle in those with chronic SCI occurs at an accelerated rate both above and below the level of lesion, suggesting a global, or systematic hormonal, process. Depressed levels of anabolic hormones (testosterone and growth hormone/ insulin-like growth factor) may partially explain the general adverse changes in soft tissue body composition in individuals with chronic SCI. These articles have shown that testosterone levels are lower with increasing duration of injury and by decade of life in those with SCI than in the able-bodied population. Growth hormone and insulin-like growth factor levels are also depressed in younger individuals with SCI. In our preclinical articles, the influence of androgens on muscle mass and signaling pathways after SCI or nerve transection has been described, as well as the antagonistic effect of androgens on the catabolic effect of glucocorticoids on muscle.
   a. Spungen AM, Wang J, Pierson RN Jr, Bauman WA. (2000).Soft Tissue Body Composition Differences in Monozygotic Twins Discordant for Spinal Cord Injury. *J Appl Physiol*. 88:1310-1315.

b. Spungen AM, Adkins RH, Stewart CA, Wang J, Pierson RN Jr, Waters RL, Bauman WA. (2003).Factors Influencing Body Composition in Persons with Spinal Cord Injury: A Cross-sectional Study. *J Appl Physiol*. 95(6):2398-407.
c. Bauman WA, Spungen AM, Flanagan S, Zhong YG, Alexander LR, Tsitouras PD. (1994). Blunted Growth Hormone Response to Intravenous Arginine in Subjects with a Spinal Cord Injury. *Horm Metab Res*. 26:149-153.
d. Bauman WA, La Fountaine MF, Spungen AM. (2014). Age-related Prevalence of Low Testosterone in Men with Spinal Cord Injury. *Journal of Spinal Cord Medicine*. 37(1): 32-39.

4. Other than some of my above noted contributions to the endocrinology and metabolism of persons with SCI, my contribution to Spinal Cord Medicine have been wide in scope in both the clinical and pre-clinical areas. In clinical medicine, my publications have been in the following areas: GI motility of the esophagus, stomach, small intestine, and, especially, the colon, with interventions to improve colonic motility and evacuation, including the novel drug combination of neostigmine+ glycopyrrolate, and strategies to improve cleansing preparation for elective colonoscopy; identifying for the first time obstructive airway disease in persons with SCI and interventions to improve function, defining restrictive airway disease in persons with complete motor SCI and strategies to improve respiratory muscle strength; defined cardiovascular autonomic dysregulation in persons with SCI and interventions to improve hemodynamics, as well as the association of cognitive deficits associated with hypotension; pressure ulcer energy requirements, healing, and intervention to heal the wound. Recently, work has been reported that describes the vertical ground reaction force and oxygen utilization while using the ReWalk exoskeleton. In the preclinical area, our work has addressed the effect of spinal cord injury on skeletal muscle. We have addressed the effect of SCI and nerve transection on muscle mass, and the effect of various anabolic or catabolic interventions on known and newly defined signaling pathways in skeletal muscle.
   a. Bauman WA, Korsten MA, Radulovic M, Gregory J. Schilero GJ, Jill M. Wecht, JM, Spungen AM. (2012). 31st G. Heiner Sell Lectureship: Secondary Medical Consequences of Spinal Cord Injury. *Top Spinal Cord Rehabil* .18 (4):354-378.
   b. Wecht JM, Bauman WA. (2013). Decentralized Cardiovascular Autonomic Control and Cognitive Deficits in Persons with Spinal Cord Injury. *J Spinal Cord Med.* 36:74-81.
   c. Bauman WA, Spungen AM, Collins JF, et al. (2013). A Randomized Clinical Control Trial of Anabolic Steroid Therapy on Pressure Ulcer Healing in Persons with Spinal Cord Injury. *Annals of Internal Medicine.* 158(10):718-726.
   d. Schilero GJ, Radulovic M, Lesser M, Bauman WA. (2014). A Center's Experience: Pulmonary Function in Spinal Cord Injury. *Lung.* 192(3):339-46.

2.1 Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/18Wf9J7w8ZFAN/bibliography/47313079/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

VA RR&D #B9212-C	**Bauman (PI)**	**07/16-06/21**
National Center Grant		**$2,250,000**
Center of Excellence for the Medical Consequences of Spinal Cord Injury		
Role: Director/Principal Investigator		
Grant # 297267	**Bauman (PI)**	**07/14 – 06/17**
Craig H. Neilsen Foundation		**$598,818**
Title: Prevention of Bone Loss after Acute Spinal Cord Injury		
Federal #2003	**Bauman (Co-Chairman)**	**10/15-9/20**
VA Cooperative Study		**$23,000,000**
Title: Exoskeleton Assisted-Walking (EAW) in Veterans with SCI: Impact on Quality of Life		
Federal #B1313-R	**Qin (PI)**	**10/14 – 9/18**
VA RR&D Service		**$885,291**

Title: Sclerostin Antagonism and the Osteocyte's Role: Prevention of Bone Loss
Role: Co-Investigator

SC130243 **Forrest & Bauman (PI)** **9/14-9/17**
Federal CDMRP/DOD $487,804 (all sites)
Title: Testosterone Combined with Electrical Stimulation and Standing: Effect on Muscle and Bone

Grant # 284196 **Wecht (PI)** **03/14 – 02/17**
Craig H. Neilsen Foundation **$593,179**
Title: Blood Pressure, Cerebral Blood Flow and Cognition in SCI
Role: Co-investigator

SC130234 **Spungen (PI)** **2015-2018**
Federal: CDMRP/DOD **$1,468,423 (4 years, all sites)**
Title: A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve
Role: Co-Investigator

#B1925-P **La Fountaine (PI)** **6/2015-5/2017**
VA RR&D SPiRE **$200,000**
Title: An Open-Label Safety and Efficacy Trial of Fenofibrate in Persons with SCI
Role: Co-Investigator

1 I21 RX001734-01A1 **Handrakis (PI)** **5/15-4/17**
RR&D Service **$196,289**
Title: Effect of Heat Exposure on Cognition in Persons with Tetraplegia
Role: Co-Investigator

1 I21 RX001915-01 **Korsten (PI)** **5/15-4/17**
RR&D Service **$193,394**
Title: Bowel Biofeedback Training to Improve Bowel Function in Individuals with SCI Role
Role: Co-Investigator

1 I21 RX001910-01 **Schilero (PI)** **8/15-7/17**
RR&D Service **$193,849**
Title: The Effect of an Oral Beta-2 Agonist on Respiratory Muscle Strength in SCI
Role: Co-Investigator

Title: Testosterone Replacement Therapy in Combination with Electrical Stimulation and Standing: Effect on Muscle and Bone in Spinal Cord Injured Males Log #SC130243 Award # W81XWH-14-2-0190

PI: Gail F Forrest PhD; William Bauman MD. **Org:** Kessler Foundation Name Here **Award Amount: $1,914,970**

Study/Product Aims

• **Primary Aim:** To determine the effectiveness and superiority of Stand Training with TRT and ES to induce beneficial changes in muscle mass compared to other combinations of these interventions.

Approach

Three sites will recruit 19 participants over 3 years or 6 subjects per year. Research participants will be randomized into one of 4 training groups: 1) Stand Training only (ST);2) ST + ES; 3) ST + TRT ; 4) ST + TRT + ES. Pre and post training outcome measures (thigh, shank, muscle volume, Quadricep muscle torque, mRNA levels for myostatin and gene expression and BMD for the proximal tibia, distal femur and hip, markers for bone formation and resorption, 3-D volumetric measurement of cortical and trabecular bone in the lower limbs, and resting energy expenditure.

Notification in November, 2015 from Abbvie that they will provide the drug and placebo at no cost to the study

- Drug/Placebo manufactured, shipped to Kessler
- All IRBs approved at Kessler and JJPMC
- Sites Commence: Kessler currently screening;
- "Kick Off Meeting": JJPMC, November 2016

Figure: Project Accomplishment: to date

Timeline and Cost

Activities CY	Yr1	Y2	Y3
IRB procedures/setup/Set up Case report from			
Drug/Placebo drug/Screening			
Screen/ Recruit 6 participants test/train			
Recruit 12			
Budget ($K)	**$84,002**	**$114,334**	

Updated: (4/25/16) Note this will be revised again in early year 3

Goals/Milestones

2014/15 Milestones– *Milestone Achieved: Local IRB approval at Kessler and JJPVAMC. Pending at UoL* Total n=56);

2016 Milestones – Drug/Placebo (Abbvie Inc) acquired; FDA IND number acquired; Equipment (stimulators) purchased for all sites; HRPO IRB approval - Kessler, JJPVAMC. HRPO UoL approval pending; Stimulation and Training protocol completed. Drug Shipped to Kessler 10/23/16; Kessler commenced study with pre screen and screen consent.

Goals 2017: "Kick Off Meeting" for JJPVAMC 11/21/16 at Kessler. Dr William Bauman will train sites on testosterone/ placebo application. Forrest and Harkema will instruct sites on protocol description per MOP. All Sites - screen, randomize, test and train

Comments/Challenges/Issues/Concerns

Significant Timeline delayed due to issues associated with obtaining Drug (see Problems and Issues in report). **Budget Expenditure to Date (**Comments/Challenges/Issues/Concerns**)

Actual Expenditure: Y1.*$84,002; Y2. $114,334* (through 14 -October 2016)

QUAD CHART